REMARKS

Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are pending in the application. Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected. Claims 39 and 42 have been objected to. The indication of the allowable subject matter of Claims 39 and 42 is noted with appreciation. Claims 36 and 47 have been amended. Reconsideration and allowance of Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 in view of the above amendments and following remarks is respectfully requested.

The Rejection of Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 Under 35 U.S.C. §§ 102(b)/103(a)

Claims 3, 4, 8, 9, 13-15, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious over Davaran et al. (Davaran et al., "Hydrophilic Copolymers Prepared From Acrylic Type Derivatives of Ibuprofen Containing Hydrolyzable Thioester Bond," *European Polymer Journal 34*(2):187-192, 1998), as evidenced by the present application, Baroni et al. (Baroni et al., "Effect of Ibuprofen and Warfarin on the Allosteric Properties of Haem-Human Serum Albumin," *European Journal of Biochemistry 268*:6214-6220, 2001), Ito et al. (Ito et al., "Control of Water Permeation by pH and Ionic Strength through a Porous Membrane Having Poly(carboxylic acid) Surface-Grafted" *Macromolecules* 25:7313-7316, 1992), and U.S. Patent No. 6,358,490, issued to Theodore et al. Withdrawal of the rejection is requested for the following reasons.

The Davaran reference is directed to hydrophilic copolymers of S-methacryloyloxyethyl-α-methyl-4(2-methylpropyl)benzene thioacetate (MOETE), a methacrylic derivative of ibuprofen. The ibuprofen moiety is separated from the methacrylic component by an oxyethylene spacer arm and a thioester bond. The water-dispersible copolymer can be prepared

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by copolymerization of MOETE with polyethylene glycol methacrylate (PEGM) (page 190, Column 2, paragraph 2).

According to the Examiner, the Davaran reference teaches hydrophilic copolymers prepared from acrylic type derivatives of ibuprofen containing hydrolyzable thioester bonds. The water-soluble hydrophilic conjugate includes a methacrylate hydrophobic component (page 189, Scheme 2), water-soluble PEG, and an ester bond linking the PEG to the methacrylate (page 190, Column 2, paragraph 2).

The Baroni reference relates to the effect of ibuprofen and warfarin on the allosteric properties of haem-human serum albumin. The Examiner has relied on the Baroni reference for the teaching that the ibuprofen is a ligand for a target.

The Ito reference is directed to a straight-pored membrane for controlling the rate of water permeation according to pH and ionic strength. The membrane was synthesized by surface-graft polymerization of vinyl monomers having a carboxylic acid substituent. The rate of water permeation through the prepared membrane changed reversibly in response to pH variation of the aqueous solution. The pH response of water permeation was controlled by changing the density and length of graft chains. The Examiner has relied on the Ito reference for the teaching that poly(methacrylic acid) disrupts polycarbonate (PC) membranes.

The Theodore reference is directed to methods, compounds, compositions, and kits that relate to pre-targeted delivery of diagnostic and therapeutic agents. The Examiner has relied on the Theodore reference for the teaching that esters and thioesters can be hydrolytically cleaved under acidic or basic conditions.

The Examiner concludes that the combined teachings of the cited references anticipate or render obvious the claimed invention. Applicants respectfully disagree.

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Claims 36, 38, 41, and 47 are the pending independent claims. Claims 3, 4, 8, 9, 13-15, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

Claims 36 and 47 have been amended. The claimed invention, as recited in amended Claims 36 and 47 and previously presented Claims 38 and 41, relates to a water-soluble hydrophilic conjugate that includes two components, a hydrophilic component and a hydrophobic component, that are linked by a pH-sensitive linkage. The pH-sensitive linkage is stable at a pH between 6.8 and 8 and is hydrolyzed at a pH less than 6.5. The hydrophobic component is endosomal membrane disruptive when released from the hydrophilic conjugate by hydrolysis of the pH-sensitive linkage. The hydrophilic component includes a polyalkylene oxide. Each of the elements noted above is recited in each of independent Claims 36, 38, 41, and 47.

Applicants submit that the independent claims' recitation that the hydrophobic component is endosomal membrane disruptive is not an intended use, but rather an element of the claim that must be afforded patentable weight.

According to M.P.E.P. 2111.02 II, whether a statement recites the purpose or intended use must be decided by whether the recited purpose or intended use results in a structural difference between the claimed invention and the prior art. When the recited purpose or intended use results in a structural difference between the claimed invention and the prior art, the recitation serves to limit the claim. See, e.g., *In re Otto*, 312 F.2d 937, 938, 136 U.S.P.Q. 458, 459 (CCPA 1963). The claimed invention requires that the hydrophobic component is endosomal membrane disruptive. The recitation leads to specific structural requirement on the hydrophobic component of the claimed conjugate. For example, as evidenced by the specification, in order to be endosomal membrane disruptive, the carboxylic acid

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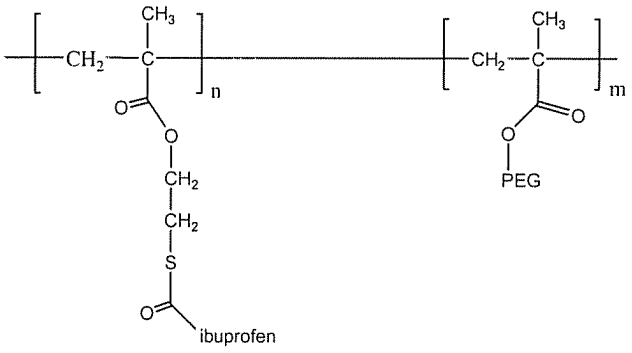
group-containing polymer serving as the hydrophobic component in the claimed conjugate must be in a sufficiently protonated form at the pH in the endosomes (between 5.0 and 6.5). This requirement imparts a structural limitation to the carboxylic acid-containing polymer useful as the hydrophobic component in the claimed conjugate. Therefore, the "endosomal membrane disruptive" recitation provides a structural limitation and must be afforded patentable weight.

Applicants submit that the cited references fail to teach or suggest a composition that includes each and every element of the claimed invention. Specifically, the cited references fail to disclose a hydrophobic component that is endosomal membrane disruptive when released from the conjugate.

The Davaran reference describes hydrophilic copolymers that include ibuprofen. The copolymers are prepared by copolymerization of a drug containing monomer (S-methacryloyloxyethyl-α-methyl-4-(2-methylpropyl)benzenethioacetate (MOETE)) and a comonomer including methacrylic acid (polyethylene glycol methacrylate). See page 188, first full paragraph, and Scheme 2 at page 189. Therefore, the Davaran reference discloses a copolymer with the following structure in which the hydrophilic component is a PEG moiety and the hydrophobic component includes a poly(methacrylic acid) moiety.



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Hydrolysis of the ester linkage intermediate the PEG group and the poly(methacrylate) backbone in Davaran's conjugate does not provide a hydrophobic component (i.e., vinyl polymer) that is endosomal membrane disruptive. Hydrolysis of Davaran's conjugate yields a poly(methacrylic acid). According to the specification, the hydrophobic component of the claimed invention is not hydrophobic at physiological pH, typically in the range of between 6.8 and 7.5, and approximately 7.4 inside cells, but becomes hydrophobic at the pH inside the endosomes (between 5.0 and 6.5) (page 10, lines 25-28). In order to be endosomal membrane disruptive, the specification states that the pKa for carboxylic acid groups on the hydrophobic component are such that they tend to be protonated at the pH range present in endosome, i.e., between 5.0 and 6.5 (page 11, lines 1-3). Therefore, the endosomal membrane disruptive ability relates to the hydrophobicity of the polymer at endosomal pH, which is affected by the combined effect of the factors including the alkyl groups of the polymer and the pKa of carboxylic acid groups of the polymer. This combined effect leads to the differences in behavior for poly(methacrylic acid), poly(ethylacrylic acid), and poly(propylacrylic acid).

The Declaration of Patrick Stayton submitted with the response filed October 31, 2007, evidences the differences in behavior for poly(methacrylic acid), poly(ethylacrylic acid), and poly(propylacrylic acid). Unlike higher alkyl poly(alkylacrylic acids), poly(methacrylic acid) is insufficiently hydrophobic to be endosomal membrane disruptive. Therefore, while poly(ethylacrylic acid) and poly(propylacrylic acid) are effective in endosomal membrane disruption, poly(methacrylic acid), which is a component of the Davaran conjugate, is not.

Furthermore, there is no apparent reason to modify Davaran's teaching to arrive at the claimed invention. The Davaran reference discloses polymeric-drug conjugates for delivering ibuprofen to solve the drug's irritant side effects on the gastro-enteric mucosa and its poor water solubility. Hydrophilic comonomers, such as methacrylic acid, methacrylamide, vinyl

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imidazole, and polyethylene glycol methacrylate, were used to copolymerize with MOETE to solubilize the drug. According to Davaran, the copolymers obtained showed water solubility sufficient for homogeneous hydrolysis of the polymeric-drug conjugates disclosed in the reference (page 190, right column). Applicants further submit that it is well known to the skilled person to use polyethylene glycol methacrylate (PEGM) as a solubilizer for hydrophobic drugs or polymers. See, for example, page 190, right column, of the Davaran reference. Because the problem associated with the solubility of the polymeric prodrug has been satisfactorily solved by using the disclosed hydrophilic comonomers and further because polyethylene glycol methacrylate (PEGM) is well-known in the field of art as a solution for solubilizing hydrophobic drugs or polymers, there is no apparent reason to modify Davaran's teaching to arrive at the claimed invention.

Contrary to the Examiner's statement, the Ito reference does not teach poly(methacrylic acid) to be endosomal membrane disruptive. The Examiner has relied on the Ito reference for the teaching that poly(methacrylic acid) disrupts polycarbonate (PC) membranes. The Ito reference discloses straight-pored polycarbonate (PC) membranes with surface grafted poly(acrylic acid), poly(methacrylic acid), and poly(ethylacrylic acid). The graft polymeric chains affect the closure of the pores of the membrane. The dissociation of the polymeric graft changes with the pH of water, which leads to the pH response of the water permeation rate through the membrane. Nowhere does the Ito reference disclose any polymer that is membrane disruptive. In addition, nowhere does the Ito reference disclose an endosomal membrane. The only membrane disclosed by the Ito reference is a polycarbonate membrane, which is neither a biological membrane nor an endosomal membrane, as recited in the claimed invention.

Regarding Dr. Stayton's declaration mentioned above, the Examiner is of the opinion that the declaration is insufficient to overcome the rejections. Specifically, the Examiner states that

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poly(methacrylic acid) meets the requirement on being "membrane disruptive" because the declaration shows at least "minimal" membrane disruption results from the use of poly(methacrylic acid) and there are no "basement" values set in the claimed invention. In addition, the Examiner claims that the declaration refers only to hemoglobin hemolysis and does not provide evidence that poly(methacrylic acid) would not disrupt other membranes. Applicants respectfully disagree.

The Examiner has taken an extreme and unreasonable view of the membrane disruption data. The claimed invention is directed to compositions and methods for delivery of therapeutic, diagnostic, or prophylactic agents for treatment or diagnostic purpose. According to the specification, "a membrane disruptive agent . . . becomes membrane disruptive following endocytosis, releasing cellular contents or releasing a therapeutic, diagnostic or prophylactic agent to be delivered" (page 6, lines 10-14). Any membrane disrupting agent disrupts the membrane or interstitial spacing such that the agent to be delivered passes through the cell or cell layer(s) (page 10, lines 9-10). The Declaration shows that poly(methacrylic acid) has a hemolysis activity close to zero. Such an extremely low hemolytic activity is meaningless in light of the definition of the term "endosomal membrane disruptive" according to the specification. Applicants submit that poly(methacrylic acid) is not endosomal membrane disruptive as defined by the specification.

Regarding the Examiner's statement that the Declaration does not provide evidence that poly(methacrylic acid) would not disrupt other membranes, applicants note that Claims 36 and 47 have been amended. The amendment clarifies that the hydrophobic component is endosomal membrane disruptive when released from the claimed conjugate. As noted in the specification, a person skilled in the art would recognize that the erythrocyte hemolysis test is predictive of disruption of endosomal membranes (page 33, lines 11-12). Therefore, the hemolysis data in the

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Declaration sufficiently supports that poly(methacrylic acid) is not endosomal membrane disruptive and thus does not satisfy the "endosomal membrane disruptive" requirement recited in the claimed invention.

For the reasons set forth above, the Davaran reference fails to describe a copolymer that releases a hydrophobic component that is endosomal membrane disruptive. There is no motivation, suggestion, or apparent reason to combine the cited references or modify Davaran's conjugate to arrive at the claimed invention. Therefore, the claimed invention is novel and nonobvious in view of the cited references. Withdrawal of the rejection is requested.

The Rejection of Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 Under 35 U.S.C. § 103(a).

Claims 3, 4, 8, 9, 13-17, 19, 34-36, 38, 40, 41, and 43-47 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of the Davaran reference in view of U.S. Patent No. 4,571,400, issued to Arnold, and Vinogradov et al. (Vinogradov et al., "Self-Assembly of Polyamine-Poly(ethylene glycol) Copolymers with Phosphorthioate Oligonucleotides," *Bioconjugate Chemistry* 9(6):805-812, 199), as evidenced by the present application, the Baroni reference, the Ito reference, and the Theodore reference. Withdrawal of the rejection is requested for the following reasons.

Claims 3, 4, 8, 9, 13-17, 19, 34, 35, 45, and 46 depend from Claim 36; Claim 40 depends from Claim 38; and Claims 43 and 44 depend from Claim 41.

The Vinogradov reference teaches cationic copolymer for DNA delivery by conjugating poly(ethylene glycol) (PEG) and polyamines: polyspermine (PSP) and polyethylenimine (PEI). The cationic copolymers include the conjugates of polyethylene glycol (PEG) and polyamines. The PEG and the polyamines are linked through a carbamate linker, i.e., -NH-COO-. The cationic copolymers are complexed to antisense oligonucleotides (PS-ODNS).

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The Arnold reference is directed to pharmaceutical compositions containing dihydrocodeine or a pharmaceutically acceptable acid addition salt thereof and ibuprofen or a pharmaceutically acceptable salt thereof that are useful in treating pain. The reference discloses a wide range of pharmaceutically acceptable carriers for use with ibuprofen.

Because neither the Vinogradov reference nor the Arnold reference discloses a polymer that is endosomal membrane disruptive at endosomal pH, the deficiencies of the teachings of the Davaran, Baroni, Ito, and Theodore references noted above with regard to independent Claims 36, 38, 41, and 47 are not cured by the teachings of the Vinogradov and Arnold references.

Because the cited references fail to teach, suggest, provide any motivation, or otherwise render obvious the claimed invention, the claimed invention is not obvious in view of the cited references. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of above amendments and foregoing remarks, applicants believe that Claims 3, 4, 8, 9, 13-17, 19, 34-36, and 38-47 are in condition for allowance. If any issue remains that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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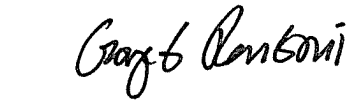

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